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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,486	06/14/1999	JOHN FRANCIS MARTIN	GJE-30	9834

7590 02/25/2004

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/297,486	MARTIN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 April 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/28/03.

Claims 1-9 are pending and are under consideration in this Office Action.

Objections Withdrawn

The objection to claim 1 over the acronym VEGF is withdrawn in view of Applicant's amendment.

Rejections Withdrawn

The rejections under 35 USC 102(a) are withdrawn in view of Applicant's showing that the cited reference did not become available until after the date of filing.

The rejections under 35 USC 103 are withdrawn because Asahara was published after the instant filing date.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting intimal hyperplasia at a site in a blood vessel in a rabbit, by periadventitial administration at the site of a DNA expression vector encoding vascular endothelial growth factor (VEGF), does not

reasonably provide enablement for treatment of any vascular disorder in any species other than a rabbit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in Paper Nos. 15 and 18.

The claimed invention is drawn to methods of inhibiting or reducing intimal hyperplasia (claims 1-9). The recited method steps require administration of a nucleic acid encoding human VEGF. The nucleic acid must be delivered periadventitially to a site where intimal hyperplasia is present or may occur. The claims require inhibition or reduction of hyperplasia. In the previous Action, the phrase "whereby intimal hyperplasia of the blood vessel is ... reduced" was interpreted as embracing reversal of existing hyperplasia. However, the specification was carefully reconsidered, and there was no evidence that Applicant wished to embrace reversal of existing hyperplasia by this phrase, but instead focused on inhibiting hyperplasia, i.e. reducing or limiting the extent limiting the extent of hyperplasia.

The specification teaches a working example in which plasmid expression vectors encoding VEGF were complexed with liposomes and delivered to the adventitial surface of a rabbit carotid artery underneath a silicone collar. It was previously shown that placement of a silicone collar on a rabbit carotid artery causes intimal hyperplasia. Injection of VEGF plasmid/liposome complexes inhibited intimal hyperplasia, but this inhibition decreased after two weeks, probably due to a loss of transient gene

expression. See the specification at page 33, lines 11-22, and page 36, lines 20-26. The specification does not exemplify reversal of existing hyperplasia.

Nucleic acid-mediated therapy

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "[s]ignificant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "[t]here is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "[t]hus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "[t]here is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

With specific respect to therapies based on the transfer of VEGF to the arterial wall, Laitinen (Pharm. Res. 4744): 251-254, 4/1998) teaches that although promising effects on cardiovascular diseases have been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, "further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full therapeutic potential of gene therapy in vascular diseases can be evaluated." See abstract. See also sentence bridging pages 252 and 253, and last sentence of CONCLUSIONS on page 253. Thus the treatment of vascular diseases in general by delivery of VEGF nucleic acids was unpredictable at the time the invention was filed.

Relevance of animal models of intimal hyperplasia to human disease and treatment

The prior art teaches that successful treatment of intimal hyperplasia in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid

metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of inhibition of intimal thickening at the precise site of VEGF expression vector administration in a rabbit model of intimal hyperplasia. See Example 1, pages 33-38. The specification teaches no example of reversal of intimal hyperplasia in any model. With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life. See paragraph bridging columns 1 and 2 on page 420. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be considered carefully in the interpretation of experimental studies. See abstract. Also, after reviewing rat, rabbit, dog, non-human primate, and pig models Muller found that it was "clear that there are major differences among the animal models, particularly in terms of the nature of arterial injury and the composition of the neointima. It could be expected, therefore, that a pharmacological therapy that is effective in one animal model may be ineffective in another species or in humans." See page 426, column 2, first full paragraph. Thus Muller clearly indicates that results in one animal model are not necessarily predictive of results in another animal model due to physiological differences between the models.

Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), reviewed the results of fifteen years of research prior to 1995, and conclude that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) further indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. In fact, the unpredictability in extrapolating results of such studies to humans was still noted in 1999 after the priority date of the instant application, when Johnson et al taught that small animal models "lacked efficacy in predicting the success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract. For these reasons, the enabled use of the claimed invention is limited to the treatment of rabbits.

In summary, at the time of the invention, those of skill in the art recognized that one could not accurately extrapolate positive results from small animal models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to provide guidance that would allow such extrapolation; the specification exemplifies only inhibition of hyperplasia in a rabbit model, and not reversal of

hyperplasia; and the specification fails to provide any working example of treatment in any organism other than a rabbit. For these reasons, one of skill in the art could not practice the claimed methods commensurate in scope with the claims without undue experimentation.

Response to Arguments

Applicant's arguments filed 11/28/03 have been fully considered but they are not persuasive.

At pages 5 and 6 of the response, Applicant argues that the rabbit is an art-accepted animal model, relying for support on Strauss (202) and Farb (2001), and asserting that if the rabbit model was not a suitable model clinical researches would not use it in their studies. This is unpersuasive because the Office has established that, at the time the invention was filed, no drug treatment developed in a small animal model had ever been used to successfully treat intimal hyperplasia in humans. As discussed in the rejection, this is because intimal hyperplasia in humans is a physiologically different process taking place in physiologically different structures than in the animal models such as the rabbit. The fact that animal models are used for research does not mean that the results obtained in these animal models will be applicable to humans, and the evidence of record shows that the results in animal models of hyperplasia both before and after the time of the invention were not applicable to humans. Applicant has presented no reasoning as to why the findings of Muller (1992), Lafont (1995), Lafont (1998), and Johnson (1999) regarding the physiological differences between various

animals and the lack of suitability of small animal models of intimal hyperplasia and restenosis should be cast aside. Applicant asserts at page 2 of the response that the Declaration of Dr. Martin, filed 11/25/02 shows that a nucleic acid encoding VEGF was successfully delivered to and expressed in pig blood vessel cells. Applicant argues that an application is not required to show that clinical efficacy is achieved, and that the Declaration is evidence of enablement.

This is unpersuasive for several reasons. First, although Applicant is not required to show that clinical efficacy is achieved, Applicant must teach how to use the invention commensurate in scope with the claims. In view of the state of the art of treating intimal hyperplasia, the unpredictability of this art, the fact that those of skill in the art find the animal models to be unsatisfactory, and the failure of the specification to provide adequate guidance to overcome these barriers to success, one of skill in the art would have to perform undue experimentation in order to practice the claimed invention commensurate in scope with the claims.

Second, although the specification teaches a working example in rabbits, the results of the experiment summarized in the Declaration suggest that the invention is inoperable in pigs. The Declaration presents the results of an experiment in which nucleic acids encoding VEGF-D were delivered at the site of surgery in pigs which had undergone surgical anastomosis of the carotid artery and internal jugular vein. The Declaration provides no statistical analysis of the results, the sample size is small, and the results indicate that the treatment may in fact increase intimal hyperplasia over time. See in particular, page 5, first sentence of paragraph 4 which indicates that at day 60

there was an increased degree of intimal proliferation/fibrosis and a reduction in luminal diameter in the groups which received VEGF-D adenovirus, when compared with the controls, and that luminal occlusion occurred only in animals treated with VEGF-D. Also, because intimal hyperplasia is known to occur in about 30% of arterial bypasses after two years (see specification at page 2, lines 10 and 11), it is not clear that an inhibition of intimal proliferation in 50% of individuals at 28 days after surgery is significant at all, particularly in view of the small sample size and the fact that after 60 days intimal proliferation and luminal occlusion increased in VEGF-treated individuals. In other words, if one would expect 70% of individuals to be unaffected by restenosis normally, it does not seem significant that intimal proliferation was inhibited in 50% of pigs. **If the described pig model generally results in a higher frequency of restenosis, such that inhibition of intimal proliferation in 50% of individuals could be considered significant, then Applicant should make this clear as it would help to overcome the enablement rejection.**

At pages 6 and 7 of the response Applicant appears to argue that because approval for a clinical trial of the claimed invention has been received from the FDA, the invention must be enabled. For support Applicant relies on MPEP 2107.03. However, this reliance is misplaced because MPEP 2107.03 is concerned with the analysis of the utility requirement, not the enablement requirement, and states for example that "[t]here is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders." Applicant's assertion that because the utility requirement is met, the enablement requirement must

also be met, is incorrect. There is no evidence or record to show efficacy of the claimed invention in humans or large mammals, furthermore the mere fact that a clinical trial is conducted with respect to safety does not address the issue og whther or not the invention has efficacy in humans. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.